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# Findings associated with recurrence of bacterial vaginosis among adolescents attending sexually transmitted diseases clinics

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## Abstract

**Study Objective—**Bacterial vaginosis (BV) is a common infection and has been associated with adverse health outcomes, including preterm birth, pelvic inflammatory disease (PID) and acquisition and transmission of HIV. There are limited data on recurrent BV in adolescents. A relationship between the frequency of BV recurrence and specific risk factors might shed light on the pathophysiology of BV and lead to targeted interventions.

**Methods—***Design*: Record-based historical clinic study. *Setting*: Adolescent visits to two sexually transmitted disease (STD) clinics between 1990-2002. *Participants*: 254 girls who had ≥ 2 episodes of BV and at least 3 clinical visits, matched on clinic attendance frequency to 254 girls with only 1 documented BV episode and 254 girls with no history of BV*. Main outcome measure*: Risk factor differences between groups. *Analysis*: Multinomial logistic regression with robust estimator of the standard errors, accounting for repeated measures.

**Results—**5,977 adolescent girls visited the clinics. 1509 (25%) had at least one episode of BV; of those, 303 (19.9%) had 2 or more BV episodes. Girls with a history of 1 BV episode and girls with a history of 2 or more BV episodes were more likely to be infected with *Trichomonas vaginalis* [OR 1.77, 95% CI: 1.17-2.67, OR 1.56, 95% CI: 1.05-2.34] and be diagnosed with PID [OR 1.50, 95% CI: 1.02-2.22, OR 2.05, 95% CI: 1.41-2.98] compared to girls with no BV history, respectively. Girls with a history of BV were also more likely to report active oral sex and lack of contraceptive use.



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**Conclusion—**Adolescent girls who attend STD clinics have a high prevalence of BV. Although the association between BV and PID is not clearly causal, when one condition is diagnosed, evaluation and counseling for the other may reduce recurrence and sequelae.

### Keywords

bacterial vaginosis; recurrent; pelvic inflammatory disease; adolescent sexually transmitted disease

## Introduction

Bacterial vaginosis (BV) is an ecological disease of the vaginal flora characterized by a shift in the vaginal microenvironment from predominately acid-producing lactobacilli to a predominance of *Gardnerella vaginalis,* anaerobes and other flora.[1;2] BV has been shown to be an independent risk factor for the acquisition of sexually transmitted infections (STIs),[3-5] acquisition and transmission of human immunodeficiency virus (HIV),[3;4;6-8] and development of pelvic inflammatory disease (PID),[9] which leads to infertility, ectopic pregnancy, and chronic pelvic pain.[10] Although the etiology of BV is unknown, a new sexual partner, vaginal douching, and lack of condom use appear to be among its strongest risk factors.[11-13] More recently, an association between receptive oral sex and BV has been suggested.[14-17]

Data from the first nationally representative sample to report on BV, the 2001 National Health and Nutrition Examination Survey (NHANES), which was based on nearly 2000 women in the United States, found the prevalence of BV was 27.4%. When evaluated by race/ethnicity, higher rates were detected in non-Hispanic blacks (50.3%) and Mexican American women (28.8%) compared to non-Hispanic whites (22.4%).[18] There are few epidemiologic data on BV in adolescents, and prevalence rates have not been widely reported. Among adolescent girls who report no history of sexual activity, up to 33% harbor BV-related organisms.[19] In one three-month observational study of 120 adolescent girls, 13% had BV during the study period and there was no difference in BV rates by history of sexual activity.[20] A prevalence rate of 34% was reported from adolescents at genitourinary medicine clinics in Manchester, UK. [21] Nonpenetrative intimate sexual contact was associated with detection of *G. vaginalis* and *Atopobium vaginae* in a study of vaginal samples from asymptomatic virginal women.[22] *A. vaginae* has been recognized as part of abnormal vaginal flora, and the metronidazole-resistant characteristics of this anaerobe may contribute to BV recurrence. [23-28]

Because the pathogenesis of BV is not known, the distinction between reinfection and relapse remains unclear.[29] Recurrent BV is common: 15-30% of women have symptomatic BV recurrence 30-90 days following therapy [30] and 70% recur within nine months. [30;31] Management of recurrent BV is not standardized,[29] and there are no data on recurrence or treatment in adolescents.

The incidence of PID is highest in the adolescent population and there are little data on the association between BV and PID in adolescents. Of the 1 million women who are diagnosed with PID each year, 70% are younger than age 25.[32] According to data collected in 1998 by the National Survey of Family Growth, 2.9% of females between the ages of 15 and 19 years reported a history of PID.[33]

In this study which was conducted in a population with high rates of BV and PID, our goal was to compare characteristics in adolescents with no history of BV, 1 episode of BV and 2 or more episodes of BV. We also sought to compare the odds of PID in these three groups of

girls. The choice of a three-group study design allowed us to determine whether adolescents with frequent disruptions in normal vaginal ecology represent a distinct population with specific behaviors and risks that differ from adolescents with fewer or no disruptions.

## Materials and methods

### Data Collection

We performed a computer record-based retrospective study of adolescent girls age 11-18 from a database of all visits to two public sexually transmitted disease (STD) clinics in Baltimore, Maryland between January 1990 and December 2002. Clinical assessment of women in the Baltimore STD clinics includes a structured interview on reproductive and STD history; voluntary HIV counseling and testing; and a directed physical examination, including pelvic examination, focusing on symptomatic complaints and STD signs. Self-reported behavioral factors referred to the 30 days before the clinic visit and included condom use (any) and contraceptive type (current), number of sexual partners, new partner (yes/no), sexual orientation, sexual exposure sites (throat, anus, vagina), patient and partner marijuana, injection drug, alcohol, cocaine use and needle-sharing (ever).

Laboratory specimens included: cervical Gram's stain, serum for syphilis serology, culture for *Neisseria gonorrhoeae* (GC) and polymerase chain reaction (PCR) for *Chlamydia trachomatis* (CT) testing after 1995 (Amplicor; Roche Diagnostic Systems, Branchburg, NJ). Before 1995, CT was diagnosed by culture. When the analysis was restricted to records dated after 1995, no differences were found in comparison between BV groups.

Vaginal wet mount included pH determination, KOH prep and microscopic evaluation for *Trichomonas vaginalis* (TV), clue cells and yeast. Vulvovaginal candidiasis (VVC) was diagnosed by the presence of yeast on KOH smear and abnormal vaginal discharge and/or vulvovaginal erythema/edema. BV diagnosis was based on 3 of 4 Amsel's criteria (vaginal discharge, pH greater than 4.5, positive whiff test, clue cells in a wet-mount preparation).[34] The majority of infections (84%) were treated with a directly dispensed and observed 2gm single dose of metronidazole. Thirteen percent were treated with a 1gm metronidazole dose per day for 7 days.

Specific data from the physical examination were available for all participants. PID diagnosis is a generated variable based on the updated 2002 CDC criteria for PID, consisting of uterine tenderness, adnexal tenderness or cervical motion tenderness, [35] which was retrospectively applied.

### Population

To be included in the analysis, girls had to have at least three visits to the STD clinic. We abstracted information on three selected groups: 254 girls with history of two or more BV infections (*2+ BV*); 254 girls with only one BV episode (*1 BV*); and 254 girls with no documented BV history (*0 BV*). The two categories of girls with BV were compared, respectively, to girls with no history of BV. Sample size was based on a 1:1:1 ratio. All eligible girls were included in the *2+ BV* group, and girls in the *1 BV* and *0 BV* groups were selected by closest match to total number of visits of girls in *2+ BV* group. 670 girls were eligible for inclusion in *0 BV* and 324 were eligible for *1 BV*. The rationale for the category distinctions was based on the outcome of interest, recurrence of BV; therefore the comparisons were made between girls with no infection, 1 infection and >1 infection.

Because those who present at STD clinics are a high risk population, they undergo full clinical examination, independent of presenting symptoms. The full clinical examination includes a bimanual examination, a speculum examination and a wet mount. In our STD

clinic, a wet mount might not be performed during a visit if the visit is for contraception purposes or for follow-up of lab results. These visits are not associated with physical examinations and they were excluded from the analysis.

The analysis was performed under an exemption from human subjects review granted by the institutional review boards of the Johns Hopkins Medical Institutions and Baltimore City Health Department.

### Data Analysis

Initial and follow-up visits were included in this analysis. Although girls with and without BV were frequency matched on total number of clinic visits, total number of clinic visits was included in multivariable analyses to control for incomplete matching and possibility of observation bias on PID diagnoses among girls who attend the clinic frequently for symptoms related to BV. Length of calendar follow-up time did not alter the multivariable findings and was not included.

A multinomial logistic regression model was used to model the population-level factors associated with a girl's history of BV recurrence. The 95% confidence intervals (CI) listed in Table 2 are based on robust estimator of the standard errors which account for the repeated measures. Variables were retained in the model if the Wald test statistic had a *P*-value ≤ 0.1. Chi-squared test or Fisher's exact test was used for categorical variables and Student's t-test was used for continuous values. Data were analyzed using STATA/SE 9.0 for Windows (Stata Corporation, College Station, Texas).

## Results

There were 12,271 visits by 5,977 adolescent girls, age 11-18, to the two STD clinics between the years 1990 and 2002. BV was diagnosed at 2,010 of these encounters (16.4% of visits) and 26% received at least one diagnosis of BV (1521 girls). Clinical criteria for PID were met at 865 encounters (7% of all visits).

Among the 762 adolescents selected for this analysis, there were 4557 visits to the STD clinics (median number of visits: 7). The average total number of visits to the clinic was 6.7 for *2+ BV*, 5.4 for *1 BV* and 5.9 for *0 BV*. Mean age for all visits was 16.2 years (SD: 1.2) and mean age at first visit to the STD clinic was 15.6 years (SD: 1.2). There were 948 BV diagnoses (508 girls), 363 CT infections (268 girls), 344 GC infections (250 girls) and 222 girls with 301 TV infections. The median number of days between BV episodes for girls in the *2+BV* group was 132.5 days. Sixty-three percent (n=160) of girls with >1 BV episode had a normal exam between BV recurrences. A diagnosis of PID was made at 371 visits (215 girls). The calendar time order of BV and PID were as follows: 123 girls had a concurrent diagnosis of BV and PID, 34 girls had a BV episode preceding the PID diagnosis, and 61 had PID preceding the diagnosis of BV. Table 1 lists demographic and behavioral information of the girls at their first visit to the clinic.

In univariable analyses, sexual risk factors including new sexual partner, lack of contraceptive use, active oral sex, cannabis use, other drugs (primarily alcohol), and two infections, VVC and TV, were more frequent in the *2+ BV* and *1 BV* groups as compared to the *0 BV* group, respectively. (Table 2) BV was not associated with incident GC or CT infections in this analysis. Additionally, rectal sex was more common in the *2+ BV* group compared to the *0 BV* group.

In multivariable models (Table 2), controlling for total number of clinic visits, history of genital infections (GC, TV, herpes simplex virus, VVC), previous PID diagnosis, new

sexual partner, oral, rectal and genital sexual exposures, cannabis and alcohol use, condom and contraceptive use, HIV infection, pregnancy, and concurrent infection (VVC, GC, CT and TV), development of PID was more common in girls categorized to the *2+ BV* group and *1 BV* group when compared to the *0 BV* group (OR 2.05, CI: 1.41-2.98, OR 1.50, CI: 1.02-2.22, respectively). Trichomoniasis and lack of contraception were more common in *2+ BV* and *1 BV* groups, and cannabis use was reported more often in the *1 BV* group compared to the *0 BV* group. Report of active oral sex was non-significantly elevated in the 2+ BV group. Although not statistically significant, the estimate for PID in the 2+ BV group was elevated as compared to 1 BV group (p=.07). No other factors were significantly different between the *2+ BV* and *1 BV* group (p>0.05).

## Discussion

With approximately 25% of adolescents diagnosed with one or more episodes of BV, our analysis suggests that BV is common among adolescents attending STD clinics in Baltimore, MD. Factors that were associated with multiple BV episodes in this analysis (trichomoniasis[36], lack of contraceptive use[37-41], and PID[9]) have also been reported to be factors in other analyses that evaluated risks associated with single episodes of BV. In addition, our analysis suggests that girls with more frequent disruptions of vaginal flora (*2+ BV* group) may be more likely than the *1 BV* group to be diagnosed with PID.

This analysis was designed to elucidate the factors that differ between girls with more frequent vaginal flora disruptions from girls with fewer or no clinically detected disruptions. This study cannot delineate a causal relationship between BV and PID since the analysis did not involve calendar time, as BV frequency *(1 BV* and *2+ BV*) was the outcome of interest. However, the relationship between BV and PID is consistent with observations reported by others studying older populations. In a cross-sectional study of BV and PID, Korn et al demonstrated in a group of women with no upper tract infection that women with BV were 15-fold more likely to have histologic evidence of endometritis than women with no history of BV. BV-associated organisms were found in endometrial cultures from 82% of women with endometritis versus 27% of women with no signs of endometritis.[42] The prospective Gynecologic Infections Follow-Through (GIFT) study demonstrated that a cluster of BV-associated microorganisms increased the risk of incident PID.[9] Previous analysis by the GIFT investigators showed no overall association between BV and incident PID,[43] suggesting that there may be subsets of women who are at increased risk of subsequent PID due to specific types of BV-associated organisms. Studies using laparoscopy have reported recovery of BV-related organisms from the fallopian tubes, even when the traditional PID-associated pathogens, *Neisseria gonorrhoeae* and *Chlamydia trachomatis*, were absent.[44] An additional correlate, furthering the association of BV with STD and PID risk, is a report by Bradshaw et al which demonstrated higher-risk sexual behavioral practices reported by women with BV in contrast to reports by women with VVC.[45]

In evaluating the associations between frequency of BV recurrence and risk factors, one hypothesis for not observing significant differences between *1 BV* and *2+ BV* is that even a single episode of symptomatic BV may lead to a chronic disruption of vaginal ecology. It is also possible that girls may not have been comfortable reporting sexual behaviors in face-to-face interviews with clinicians. The clinics do not routinely use audio computer assisted self interview (ACASI) in clinical care; this technology has demonstrated higher reporting rates of sensitive behaviors in our clinics. [46] Alternatively, girls may not have returned to the STD clinic for care, and intervening episodes of BV, particularly asymptomatic ones, may have been missed. Although this was not a structured cohort study with scheduled follow-up intervals, the population of inner-city girls who use the free Baltimore City Health

Department STD clinic services often do so exclusively without accessing other clinical care venues (as suggested by the frequency of visits to these clinics).

The available clinical data allowed us to retrospectively apply the revised 2002 CDC criteria for PID[35] to this cohort. Although the specificity of the diagnosis of PID using these criteria is lower, the results are more relevant to current standards. The gold-standard for diagnosing PID continues to be laparoscopy which is invasive and expensive. Girls with more frequent clinic visits may be more likely to have PID detected on physical examination leading to an outcome identification bias. To account for this, we controlled for total number of visits in multivariable analyses and selected girls in the *1 BV* and *0 BV* groups to match as closely as possible on total number of clinic visits of the *2+ BV* group.

Vaginal douching is another potential risk factor for BV and PID,[1;47-50] however data on genital cleansing practices in this population of adolescents were not available. In a systematic sample of 292 adult women attending the Baltimore City STD Clinics from September 2001 to January 2002, 71% reported current douching. Women reported they used their first douche at a median age of 15-18 years.[51]

There was a high prevalence of alcohol and cannabis use in this population. These may be markers of overall increased risk-taking behaviors in general, rather than a true biological association with BV. However, care in counseling teenagers with BV, specifically about alcohol use, is warranted, as alcohol may interact with oral metronidazole which is often used in the treatment of BV.

A strength of our study design is the categorization of the outcome by BV recurrence frequency which allowed girls to fluctuate on BV status over time. Because of these fluctuations, longitudinal models that evaluate the risks for BV are complicated by the frequent transition of exposure windows. A single vaginal flora assessment on a given day in the menstrual cycle may not have predictive power for risk modeling. A better approach may be to rely more on measures of chronicity. Prospective studies with frequent sampling for BV are needed to better elucidate the time-related associations among BV, STDs and PID.

An additional strength of our study include a large patient base from which to draw cases and controls, a population of patients in which the diseases studied are prevalent. Consistency of patient treatment in clinics driven by protocols also contributed to study validity.

Elucidating risk factors in adolescents, as well as potential co-morbidity in the setting of recurrence, provides clinicians with valuable background for counseling patients. Prevention strategies for BV and PID overlap as modifiable risk factors for both include condom use, discontinuation of douching, smoking cessation, and engaging with fewer sex partners.[52] As for treatment of recurrent BV, investigators are still determining effective regimens. The use of probiotics to replace lactobacilli (vaginal or oral), the use of acidifying gels to maintain vaginal pH $\leq$ 4.5, boric acid and tinidazole treatment, and preventing overgrowth of BV-associated bacteria with suppressive doses of antibiotics are methods still in need of development.[53-57]

In summary, BV and its recurrence are common in adolescents attending STD clinics. This susceptible population should be screened for BV and those with disrupted vaginal ecology may benefit from intervention strategies aimed at preventing both BV and PID. Prospective studies that further our understanding of the relationship between microbial vaginal ecology and PID may lead to strategies that prevent the devastating consequences of PID in adolescents.

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## Synopsis

Bacterial vaginosis is common among adolescent STD clinic attendees and its recurrence may be associated with a higher risk for pelvic inflammatory disease.

## Table 1

Characteristics of the three groups of adolescent girls at each girl's respective first STD clinic visit, Baltimore, MD, 1990-2002 (n=762)

| | (1) *0 BV (%)* (n=254) | (2) *1 BV (%)* (n=254) | (2) vs (1) p-value[a] | (3) 2+ *BV (%)* (n=254) | (3) vs (1) p-value[a] |
|---|---|---|---|---|---|
| Mean age (SD) | 15.59 (1.17) | 15.78 (1.12) | 0.07 | 15.50 (1.28) | 0.40 |
| Mean number of visits per participant (SD) | 5.86 (2.79) | 5.41 (2.96) | 0.08 | 6.67 (4.87) | 0.02 |
| Race: | | | | | |
| Non-Hispanic white (%) | 5 (1.97) | 4 (1.57) | 0.35 | 1 (0.39) | 0.33 |
| Non-Hispanic black (%) | 248 (97.64) | 245 (96.46) | | 251 (98.82) | |
| Reason for visit: | | | | | |
| Symptoms | 72 (28.35) | 138 (54.33) | 0.00 | 145 (57.09) | 0.00 |
| Contact of STD patient | 15 (5.91) | 22 ( 8.66) | 0.22 | 31 (12.20) | 0.01 |
| Contacted because of positive | | | | | |
| Gonorrhea, Chlamydia, or Syphilis culture | 11 (4.33) | 9 (3.54) | 0.65 | 16 (6.30) | 0.32 |

[a] p-value compared to *0 BV* group, t-test or Fisher's exact for continuous or chi-squared test for categorical variables

## Table 2

Risk factors of adolescent girls in the *1 BV* and 2+ *BV* groups compared to girls in the *0 BV* group, Baltimore, MD, 1990-2002 (n=762)

| | 1 BV episode | | | | 2 or more BV episodes | | | |
|---|---|---|---|---|---|---|---|---|
| | univariable OR[a] | 95% CI OR[a] | aOR OR[b] | 95% CI | univariable OR OR[a] | 95% CI OR[a] | aOR[b] | 95% CI |
| **Sexual risk behavior (previous 30 days)** | | | | | | | | |
| New sexual partner | 2.31 | 1.66-3.22 | 1.33 | 0.92-1.91 | 1.97 | 1.42-2.73 | 0.87 | 0.60-1.24 |
| Oral sex (active) | 2.41 | 1.60- 3.61 | 1.30 | 0.84-2.02 | 3.76 | 2.48-5.72 | 1.47 | 0.97-2.23 |
| Genital exposure | 2.54 | 2.07-3.13 | 0.79 | 0.51-1.23 | 3.79 | 3.04-4.74 | 0.94 | 0.60-1.46 |
| Rectal sex | 1.61 | 0.82-3.15 | 0.63 | 0.31-1.27 | 2.49 | 1.19-5.23 | 0.58 | 0.30-1.14 |
| **Contraceptive Use** | | | | | | | | |
| None | 1.75 | 1.33-2.32 | 1.87 | 1.28-2.71 | 2.49 | 1.92-3.24 | 2.09 | 1.45-3.02 |
| **Self-reported behaviors** | | | | | | | | |
| Cannabis use | 2.04 | 1.40-2.99 | 1.51 | 0.98-2.31 | 2.05 | 1.39-3.04 | 1.28 | 0.83-1.99 |
| Other drug, primarily alcohol | 1.61 | 1.13-2.29 | 1.13 | 0.77-1.66 | 1.87 | 1.32-2.64 | 1.25 | 0.86-1.84 |
| **Diagnosis at current visit** | | | | | | | | |
| Pelvic inflammatory disease | 1.75 | 1.19-2.57 | 1.50 | 1.02-2.22 | 2.30 | 1.57-3.35 | 2.05 | 1.41-2.98 |
| Candidiasis | 1.74 | 1.28-2.36 | 1.18 | 0.86-1.61 | 1.93 | 1.45-2.57 | 1.13 | 0.83-1.54 |
| Gonorrhea | 0.77 | 0.54-1.10 | 0.82 | 0.58-1.17 | 0.79 | 0.57-1.11 | 1.01 | 0.73-1.41 |
| Chlamydia | 1.33 | 0.91-1.94 | 1.26 | 0.84-1.89 | 0.95 | 0.65-1.38 | 1.00 | 0.67-1.49 |
| Trichomonas | 2.66 | 1.80-3.93 | 1.77 | 1.17-2.67 | 2.60 | 1.79-3.77 | 1.56 | 1.05-2.34 |

[a] OR, odds ratio; CI confidence interval

[b] aOR, adjusted odds ratio; Multivariable analysis controlled for all variables listed and in addition, age, current pregnancy status, HIV infection, selfreported previous sexually transmitted infections, contemporaneous gonorrhea, chlamydia and trichomonas infection, condom use in the past 30 days (ever), and number of follow-up visits.